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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,010	12/30/2003	Randolph J. Noelle	58281US004	7654

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/748,010	NOELLE ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *6,7,11-48 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-10,49-53 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-57* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The species election of Toll-Like Receptor is being withdrawn after further consideration.

Applicants' request for withdraw of the species election of TNF/R agonist to consist of both CD40 and 4-1BB agonists is granted.

As a result, claims 1-5, 8-10 and 49-53 and 55-57 are currently under examination.

Response to Arguments

The rejection of claims under 35 USC 12, first paragraph, has been recast to address the amendments to the claims.

The rejection of claims under 35 USC 103 is withdrawn in view of the amendment adding the requirement of synergistic action of the agonists.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8-10, 49-53 and 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require a CD40 or 4-1BB agonist. The specification defines an "agonist" as a compound that directly binds and activates the receptor or indirectly activates it by (i) forming a complex with another molecule which binds the receptor or (ii) causing the modification of another compound so that the other compound directly binds and activates the receptor (p. 4, lines 1-8). There are CD40 and 4-1BB agonist known that can directly bind and activate the receptor, *e.g.*, CD40L, 4-1BBL as well as agonist antibodies, which meet the written description provision of 35 USC 112, first paragraph. However, the claims are directed to or encompass

compounds or molecules that complex with or modify other products that then activate the receptor. None of these "indirect" agonists meet the written description provision of 35 USC 112, first paragraph. There is no disclosure of such agonists nor does the prior art describe such agonists for CD40 or 4-1BB.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only agonists that directly bind CD40 or 4-1BB and thereby activate the receptor, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claims 1-5, 8-10, 49-53 and 55-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CD40 agonist which is CD40L or an anti-CD40 agonist antibody and for a 4-1BB agonist which is 4-1BBL or an anti-4-1BB agonist antibody, does not reasonably provide enablement for other CD40 or 4-1BB agonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the reasons set forth in the previous Office action directed toward nonenablement of CD40 agonist in particular and TNF/R agonists in general and for the following reason addressing the amendment

to the claims: the claims now limit the TNF/R agonist to an agonist of CD40 or 4-1BB. Nevertheless, agonists of 4-1BB has the same enablement issues as those of CD40 previously addressed.

As amended, the claims are drawn to compositions: an immunostimulatory combination or a vaccine, which comprise a CD40 or 4-1BB agonist. While the natural ligand of each receptor is known, as are agonist antibodies, there is no disclosure of an agonist of these receptors which does not itself bind the receptor but which functions by complexing with another compound that binds and activates the receptor or by causing modification of another compounds which can then bind and activate the receptor. Nor does the prior art describe such agonists for CD40 or 4-1BB. The structure of such an agonist is not disclosed nor are any characteristics aside from its function of activating the receptor and somehow interacting with the compound or molecule. Therefore, the claims are like single means claims.

A single means claim, *i.e.*, where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. § 112, first paragraph. *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.). When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. Although the court in *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993) did not decide the enablement issue, it did suggest that a claim directed to all DNAs that code for a specified polypeptide is analogous to a single means claim. (MPEP § 2164.08)

As a result, the invention is not commensurate in scope with the claims since they encompass not only those agonists which directly bind CD40 or 4-1BB, but also those which indirectly produce a cellular response through the receptor. The specification has not taught how to make those agonists which act indirectly, nor does the prior art provide examples and/or guidance about which products would reasonably be expected to act as indirect CD40 or 4-1BB agonists, so that the skilled artisan could make representative number of them without undue experimentation.

Note that claims 8 and 55 say the 4-1BB agonist comprises an agonist antibody but does not required that it is an anti-4-1BB agonist antibody. Similarly claim 56 recites a CD40 agonist comprising an agonistic antibody but does not require that it be an anti-CD40 antibody. Also note that claim 9 says the CD40 agonist comprises an anti-CD40 antibody but does not require it to be an agonist antibody. If the antibodies of these claims are not anti-CD40 or anti-4-BB agonist antibodies, they are not enabled for the reasons discussed above.

Applicants argue that the disclosure enables one skilled in the art to make and/or use the claimed invention across the full scope of CD40 and 4-1BB agonists because the disclosure exemplifies CD40 agonist synergism with TLR agonists. Additionally, 4-1BBL with a TLR agonist also generated a synergistic CD8+ T cell response. The argument has been fully considered, but is not persuasive. The specification shows the activity of an anti-CD40 agonist antibody and 4-1BBL. Both these agonist act directly on the receptor they activate. There is no showing of a CD40 or 4-1BB agonist in the specification or prior art that acts indirectly on these receptors to enable synergism with a TLR agonist as discussed in the rejection above.

Claims 1-5, 8-10, 49 and 55-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agonist of TLR1, TLR2, TR3, TLR4, TLR5, TLR6, TLR7, TLR8 or TLR9 does not reasonably provide enablement for an agonist of TLR10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims encompass agonists of TLR1-TLR10; however, no ligand is known for TLR10. There has been extensive searching for a TLR10 ligand, including an antibody that could affect TLR10 activity, but to date none have been discovered. As stated by Hasan et al. in 2005 (J. Immunol. 174:2942-2950, IDS filed 2/2/07), " TLR10 remains the only orphan member among the human TLRs." Because the specification, prior art and even post-filing evidence do not provides an example of a TLR10 ligand or agonist, and the information available to the skilled artisan would not allow the prediction of the structure of an agonist, it would require undue experimentation to make a TLR10 agonist.

Applicants argue that the disclosure enables one skilled in the art to make and/or use the claimed invention across the full scope of TLR agonists. A brief listing of agonist of TLR1-TLR9 is provided (p. 12 of response) and Examples in the specification are presented with TLR1-TLR4 and TLR6, TLR7 and TLR9. Even though TLR10 has not been shown experimentally to synergize with a CD40 agonist, Applicants argue one would expect it would since it is functional and signals through the MyD88-dependent pathway common to TLRs. The argument has been fully considered, but is not persuasive. Just for the reasons that TLR10 has no known agonist, though one has been searched for over many years, one could not make a TLR10 agonist without undue experimentation (see the above rejection and discussion of Hasan et al. therein).

Applicants argue that the specification provides methods for determining whether a compound is an agonist of any particular TLR (*e.g.*, p. 8-9). The argument has been fully considered, but is not persuasive. For the reasons discussed above, namely the inability of scientist to identify an agonist of TLR10 despite the identification and synthesis of ligands for TLR1-TLR9, it is maintained that it would require undue experimentation to make the invention commensurate with its full scope.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8-10, 49-53 and 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because the definition of an "agonist" in the specification (p. 4, lines 1-8) is so broad, without any structural limitations, as to make the metes and bounds of the claims unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Krug et al. (Eur. J. Immunol, 31:3026, Oct. 2001).

Krug et al. teaches an immunostimulatory combination of CD40 ligand (CD40L) with CpG oligodeoxynucleotide (ODN), which is a TLR9 agonist. The combination synergistically activates plasmacytoid dendritic cells (PDC) (*e.g.*, p. 3027 and p. 3029, first paragraphs of each col. 2). It also induced a large increase in IFN-γ-producing T cells (Fig. 9).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 49, 51, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krug et al. as applied to claims 1-4 and 9 above, and further in view of Melief et al. (Immunological Rev., 188:177, Oct. 2002, cited by Examiner 9/15/06).

Krug et al. teaches an immunostimulatory combination of CD40 ligand (CD40L) with CpG oligodeoxynucleotide (ODN), which is a TLR9 agonist and mimics bacterial DNA. The

combination synergistically activates plasmacytoid dendritic cells (PDC) (*e.g.*, p. 3027 and p. 3029, first paragraphs of each col. 2). It also induced a large incraese in IFN-γ-producing T cells (Fig. 9). Krug et al. also teach (p. 3026, last paragraph), "As a vaccine adjuvant, CpG DNA is at least as effective as the gold standard complete Freund's adjuvant (CFA), but has higher Th1 activity and lower toxicity...." They also discuss the importance of "CD40 ligation" in obtaining significant PDC responses (p. 3033, col. 1, third and fourth paragraphs), stating (last two sentences beginning p. 3033): "Our data support the view that PDC in the presence of the appropriate microbial stimulus and CD40 ligation induce an IL-12-dependent Th1 response.... Selective amplification of T cell-derived signals might explain why CpG ODN acts as a potent Th1 adjuvant *in vivo* without causing major toxicity or autoimmunity." Krug et al. do not teach a vaccine comprising an agonist of TLR9 and CD40.

Melief et al. teach therapeutic anticancer vaccines. They also teach that an agonistic monoclonal antibody against CD40 turned a preventative vaccine against human papilloma virus 16 into a therapeutic vaccine in mice and in some cases, administration of an anti-CD40 antibody alone was sufficient to completely eradicate tumors (p. 178, col. 2, 2nd paragraph). Finally,

> "It is now possible to design entirely synthetic vaccines that provide both the proper antigenic and accessory signals for induction of full scale CTL [cytolytic T-lymphocyte] effector burst as well as CTL memory. These signals employ molecularly defined innate immunity receptors such as those belonging to the TLR family, and/or adaptive immunity receptors such as CD40 or Fc receptors (*Table 1*). In cancer, it is precisely the triggering of these receptors that is lacking.... Provision of the proper TLR ligands from the microbial realm will drastically enhance these abortive responses and turn them into strong tumoricidal effector responses capable of eradicating established cancers. Both for preclinical research and for preparation and application of clinical grade vaccines, entirely synthetic formulations offer marked advantages. Rather than rely on poorly defined immune system triggers, such as recombinant vectors and adjutants without molecularly defined function, the novel generation of TLR ligand-mimicking adjuvants induces very precise signal transduction pathways in professional APC [antigen-presenting cell] that, moreover, can be further manipulated for desired effect by very precise changes in the ligands."

CpG-ODN adjuvant provided immunity against human papillomavirus-induced mouse tumors (p. 181, first full paragraph).

It would have been obvious to the artisan of ordinary skill at the time the invention was made to have a vaccine comprising the TLR9 agonist, CpG ODN, in combination with an anti-CD40 agonist antibody in order to induce an immune response against an antigen when in the form of a vaccine. The vaccine would have been obvious and desirable because Krug et al. showed that CpG ODN acted synergistically with CD40L to stimulate a T cell response. Krug et al. also say that CpG ODN is a potent Th1 vaccine adjuvant and notes that CD40 ligation is important for the synergism, implying that what is important for synergism is the CD40 activation instead of what activates CD40. Melief et al. showed the use of a CD40 agonist antibody enhanced activity of a viral vaccine. The CD40 agonist antibody necessarily ligated CD40. Melief et al. also said that synthetic TLR ligands are very useful in vaccines, allowing for induction of "very precise signal transduction pathways", and in combination with a CD40 agonist should provide a means for destroying established cancers. A specific example was provided for CpG-ODN, which may functions as a tumor antigen, viral antigen and bacterial antigen according to Krug et al. and Melief et al. For these reasons the invention is obvious.

Art

The art made of record and not relied upon is considered pertinent to applicant's disclosure. Ahonen et al. (J. Ex. Med., 199(6) :775-784, 15 Mar 2004) is a post-filing reference by the inventors and other which shows synergy of a TLRs 2/6, 3, 4, 7 and 9 agonist when combined with a CD40 agonist in stimulation of $CD8^+$ T cells. Even though TLR8 agonist synergism with a CD40 ligand was not examined by Ahonen et al., because TLR8 shares agonists with TLR7, one skilled in the art would reasonably have expected synergism from the combination.

Myer et al. (PNAS 100(9) :5348-5353, 29 Apr. 2003) is post-filing art that supports the ability of a 4-1BB agonist with a TLR agonist (specifically TLR3 and/or TLR4) to "massively enhance specific T cell clonal expansion *in vivo*..." (*e.g.*, p. 5348, col. 2, first full sentence)

Edwards et al. J. Immunol. 169:3652-3660, 01 Oct. 2002, discuss the role of CD40 tirggering in dendritic cell responses to microbial antigens, including TLR2 angonists,

concluding (p. 3655, sentence bridging cols. 1-2) "These resutls demonstrate that TLR2 and My D88 signaling mediate PPD condition of DC for CD40-triggered IL-12 p70 production...." Edwards et al. do not suggest synergist activity of a CD40 agonist and TLR2 agonist.

Alternative Names

CD40 is also known as TNFRSF5. CD40L is also known as CD154 or TNFSF5. 4-1BB is also known as TNFRSF9 or CD137. 4-1BBL is also known as CD137 ligand or TNFSF9.

Conclusion

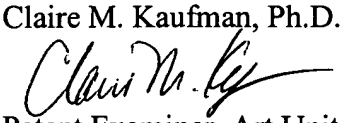
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

April 12, 2007